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(71) Applicant

**Istituto Gentili SpA (Italy),
Via Mazzini 112, Pisa, Italy**

(72) Inventor

Sergio Rosini

(74) Agent and/or Address for Service

**Batchellor Kirk & Eyles,
2 Pear Tree Court, Farringdon Road, London
EC1R 0DS**

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Pharmaceutical Codex 11th Editn 1979 page 907 re
"Effervescent tablets" page 727 re "Effervescent
powders" and page 198**

(58) Field of search

A5B

(54) **Effervescent preparations containing diphosphonates**

(57) Pharmaceutical formations for the administration of diphosphonates for treating impaired conditions of the phosphorus-calcium metabolism, having a better absorption degree comprise diphosphonates in excipients suitable to give effervescent solutions e.g. citric acid/sodium carbonate/sodium bicarbonate. The formulations may be powders, granules or tablets and the phosphonates are preferably sodium etidronate, dichloromethylene diphosphonate, and amino-hydroxy-propan-butan-, pentan-, hexan-diphosphonate.

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SPECIFICATION

New pharmaceutical forms containing diphosphonates

- 5 The present invention refers to new pharmaceutical forms for the administration of diphosphonates. 5

The diphosphonates are a class of compounds recently introduced in therapeutic practice for treating and correcting impaired conditions of phosphorus-calcium metabolism.

- 10 Several papers have been published on the activity of diphosphonates (sodium ethidronate, dichloromethylene-diphosphonates and amino-hydroxy-propan-, butan-, pentan-, hexan-diphosphonate and the like) in the inhibition of bone reabsorption which is enhanced in an abnormal way in many bone diseases such as Paget's bone disease, bone tumors, bone metastasis induced by tumors, as well as in osteoporosis or in hyperparathyroidism etc. 10

- 15 Recently some diphosphonates have been used in the treatment of metastatic osteolysis. This new possibility of application derives from specific studies on the action of diphosphonates on the bone reabsorption in tumoral osteolysis, studies started in 1977 and subsequently applied to animals (Jung 1979) and, finally, to humans. 15

The use of diphosphonates as bone reabsorption inhibitors has however noticeable drawbacks, essentially connected with the absorption, which can be summarised as follows:

- 20 (a) low absorption degree for oral administration; 20
(b) inconstant absorption and changing in time and from patient to patient.

- These difficulties of absorption involve therefore, in oral administration, the use of high dosages, with consequent difficulties in the formulation of capsules, tablets etc., containing very high amounts of active principle and with noticeable discomfort for patients subjected to continuous administrations of capsules and tablets inducing disturbing gastralgies. 25

It has been now surprisingly found that the diphosphonates, administered in the form of effervescent formulations, exhibit higher activity than that induced by equal concentrations of the product in the form of tablets.

- 30 This is probably due to an enhanced gastrointestinal absorption induced by the effervescent form, as appears from the presence, in the patients urine, of phosphate concentrations higher than those found after administration of diphosphonates as tablets. 30

It is therefore evident that it is possible to reduce dosages and administration frequency, by means of the effervescent formulations, allowing therefore an easy treatment which is well tolerated by patients.

- 35 The concentrations of the diphosphonates can differ according to the intended use and according to the intrinsic activity degree of the different diphosphonates and they will range from 5 to 3000 mg for monodose sachets and monodose effervescent tablets. 35

The following non limitative examples further illustrate the compositions according to the invention

- 40 **EXAMPLE 1** 40

Effervescent tablets

45	Alkylidene-diphosphonic acids	mg	1000	45
	anhydrous citric acid	mg	500	
	anhydrous sodium carbonate	mg	375	
	sodium bicarbonate (granular)	mg	525	
	natural orange flavour	mg	5	
50	sodium benzoate	mg	95	50
Total		mg	2500	

EXAMPLE 2

Effervescent granular			
5			5
	Alkylidene-diphosphonic acid	mg 1000	
	anhydrous sodium carbonate	mg 150	
	sodium bicarbonate	mg 280	
	saccharose	mg 3888	
10	sodium saccharinate	mg 20	10
	anhydrous citric acid	mg 700	
	anhydrous orange flavour	mg 460	
	natural orange flavour	mg 2	
15	Total	mg 6500	15

EXAMPLE 3

20	Monodose sachet			20
	Alkylidene-diphosphonic acid	mg 200		
	sodium carbonate	mg 30		
25	sodium bicarbonate	mg 55	25	
	sodium saccharinate	mg .5		
	anhydrous citric acid	mg 140		
	anhydrous lemon flavour	mg 90		
	saccharose	mg 229		
30	natural lemon juice	mg 1	30	
	Total	mg 750		

35 CLAIMS

1. Pharmaceutical formulations, suitable for the treatment of bone diseases containing diphosphonates, intended to be administered by the oral route, which formulations are in form of monodose sachets or tablets containing diphosphonates in excipients suitable to give effervescent solutions.
2. Formulation according to claim 1 containing from 5 to 3000 mg of active principle.
3. Formulations according to claim 1 or 2 suitable for use in the treatment of tumoral osteolysis or hyperparathyroidism conditions.
4. A pharmaceutical formulation substantially as described in Example 1, 2 or 3.
5. For use in the treatment of bone diseases, pharmaceutical formulations according to any one of the preceding claims.